COMPARATIVE ANALYSIS OF NOTIFIED HAND, FOOT, AND MOUTH DISEASE CASES BETWEEN KELANTAN AND PENANG

DR AINA SYAZWANI BINTI AZIZ

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by

DR AINA SYAZWANI BINTI AZIZ

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LIST OF SYMBOLS

=	Equals to
≥	More and equal than
<	Less than
α	Alpha
β	Beta
n	Number of samples
m	Ratio between two groups
χ^2	Chi-square
df	Degree of freedom

LIST OF ABBREVIATIONS

CDCIS	Communicable Disease Control Information System
CI	Confidence interval
CV-A6	Coxsackievirus A-6
CV-A10	Coxsackievirus A-10
CV-A16	Coxsackievirus A-16
EV 71	Enterovirus 71
HFMD	Hand, Foot, and Mouth Disease
IR	Incidence rate
IQR	Interquartile range
JKNK	Jabatan Kesihatan Negeri Kelantan
JKNPP	Jabatan Kesihatan Negeri Pulau Pinang
MOH	Ministry of Health
NMRR	National Medical Research Registry
OR	Odd Ratio
WHO	World Health Organization

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ANALISIS PERBANDINGAN KES PENYAKIT TANGAN, KAKI DAN MULUT YANG DILAPORKAN ANTARA KELANTAN DAN PULAU PINANG

ABSTRAK

Latar Belakang: Penyakit Tangan, Kaki dan Mulut (HFMD), yang disebabkan oleh enterovirus seperti EV 71 dan CV-A16, masih menjadi isu kesihatan awam yang penting di Malaysia, kerana ianya memberi kesan terbesar kepada kanak-kanak. Walaupun terdapat pelbagaai usaha yang dilakukan untuk menurunkan beban penyakit HFMD, kadar kejadian terus meningkat dari semasa ke semasa. Oleh itu, penyelidikan lanjut mengenai perbezaan serantau dan faktor risiko yang berkaitan perlu dijalankan.

Objektif: Kajian ini bertujuan untuk menganggar kadar kejadian dan faktor risiko kes HFMD yang dilaporkan antara negeri Kelantan dan Pulau Pinang dari tahun 2017 hingga 2021. Secara khusus, ia bertujuan untuk mengenal pasti perbezaan dalam kadar kejadian dan pengedaran kes mengikut umur, jantina, dan kaum.

Metodologi: Reka bentuk kajian keratan rentas perbandingan telah digunakan, menggunakan data sekunder daripada Sistem Maklumat Kawalan Penyakit Berjangkit (CDCIS) e-Notifikasi. Populasi kajian merupakan semua kes HFMD yang dilaporkan di Kelantan dan Pulau Pinang dari tahun 2017 hingga 2021. Analisis statistik, termasuk ujian *chi-square*, dilakukan menggunakan perisian R untuk membandingkan kadar kejadian dan faktor demografi antara kedua-dua negeri.

Keputusan: Dari tahun 2017 hingga 2021, sebanyak 18,243 kes HFMD dilaporkan, yang mana 7,846 kes dilaporkan di Kelantan manakala 10,397 kes di Pulau Pinang. Kadar kejadian purata adalah lebih tinggi di Pulau Pinang (1.18 per 1,000 populasi)

berbanding Kelantan (0.49 per 1,000 populasi). Kejadian tertinggi berlaku dalam kalangan kanak-kanak berumur 0-4 tahun di kedua-dua negeri, dengan perbezaan yang signifikan dalam peredaran umur ($\chi 2$ (3) = 303.48, $p < 0.05$). Jantina lelaki lebih berisiko untuk dijangkiti HFMD berbanding perempuan di kedua-dua negeri, dengan perbezaan yang signifikan secara statistik ($\chi 2$ (1) = 6.885, $p = 0.009$). Kumpulan etnik Melayu melaporkan bilangan kes tertinggi di kedua-dua negeri, namun terdapat perbezaan yang ketara jika dibandingkan dengan lain-lain kaum ($\chi 2$ (4) = 4290.40, $p < 0.05$).

Kesimpulan: Kajian ini mendedahkan perbezaan serantau yang ketara dalam kadar kejadian HFMD dan faktor demografi antara negeri Kelantan dan Pulau Pinang. Penemuan ini menekankan keperluan intervensi kesihatan awam yang bersasar, dengan tumpuan diberikan secara khusus kepada kanak-kanak serta penjaga dan menggunakan pendidikan kesihatan yang komprehensif dan bersesuaian untuk kumpulan etnik yang berbeza. Sistem pengawasan dan kawalan penyakit perlu dipertingkatkan bagi memastikan pengesanan awal dan pengurusan wabak HFMD secara berkesan dapat dilakukan.

KEYWORDS: Penyakit Tangan, Kaki dan Mulut, Kelantan, Penang, kadar kejadian, epidemiologi, factor risiko, kesihatan awam

COMPARATIVE ANALYSIS OF NOTIFIED HAND, FOOT, AND MOUTH DISEASE CASES BETWEEN KELANTAN AND PENANG

ABSTRACT

Background: Hand Foot and Mouth Disease (HFMD), primarily caused by enteroviruses like EV 71 and CV-A16, remains a significant public health issue in Malaysia, particularly affecting children. Despite extensive efforts to manage HFMD, the incidence rate continues to rise, necessitating further investigation into regional differences and associated risk factors.

Objectives: This study aims to estimate the incidence rates and risk factors of notified HFMD cases between the states of Kelantan and Penang from 2017 to 2021. Specifically, it seeks to identify differences in incidence rates and the distribution of cases by age, gender, and race.

Methodology: A comparative cross-sectional study design was employed, utilizing secondary data from the Communicable Disease Control Information System (CDCIS) e-Notification. The study population included all notified HFMD cases in Kelantan and Penang from 2017 to 2021. Statistical analyses, including chi-square tests, were conducted using R software to estimate incidence rates and demographic factors between the two states.

Results: From 2017 to 2021, 18,243 HFMD cases were reported, with 7,846 in Kelantan and 10,397 in Penang. The average incidence rate was higher in Penang (1.18 per 1,000 population) compared to Kelantan (0.49 per 1,000 population). The incidence was highest among children aged 0-4 years in both states, with significant differences in age distribution ($\chi 2$ (3) = 303.48, $p < 0.05$). Males had a higher

prevalence of HFMD in both states, with a statistically significant difference in gender distribution ($\chi 2$ (1) = 6.885, p = 0.009). The Malay ethnic group had the highest number of cases in both states, but significant differences were observed in racial distribution ($\chi 2$ (4) = 4290.40, $p < 0.05$).

Conclusion: The study reveals significant regional differences in HFMD incidence rates and demographic factors between Kelantan and Penang. The findings highlight the need for targeted public health interventions, particularly focusing on young children and incorporating comprehensive health education tailored to different ethnic groups. Enhanced surveillance systems are crucial for early detection and effective management of HFMD outbreaks.

KEYWORDS: Hand, Foot, and Mouth Disease, Kelantan, Penang, incidence rate, epidemiology, public health, risk factors

CHAPTER 1

INTRODUCTION

1.1 Background

Since the 1970s, there have been reports of outbreaks caused by EV 71 infection worldwide. Most of these cases involve children and are characterized by symptoms frequently seen in hand, foot, and mouth disease (HFMD), including fever, skin eruptions on the hands and feet, and vesicles in the mouth. Several cases also exhibited involvement of the central nervous system and/or pulmonary oedema, leading to fatalities. There are several countries that had reported a widespread of HFMD epidemics in the Western Pacific Region such as Australia, Brunei Darussalam. China, Japan, Malaysia, Singapore, Vietnam, the Republic of Korea, and Mongolia (WHO, 2011).

HFMD is a result of enteroviruses, which are made up of a single-stranded, positive-sense RNA and belong to the *Picornaviridae family*. Human enteroviruses have been categorized into multiple classes based on their ability to cause disease in humans and laboratory animals, as well as the impact they have on cells. The subgroups consist of polioviruses (3 serotypes), coxsackievirus A (23 serotypes), coxsackievirus B (6 serotypes), echoviruses (28 serotypes), and other enteroviruses (Solomon *et al.*, 2010). The primary etiological agents responsible for HFMD are EV 71 and CV-A16. Nevertheless, there is a rising incidence of HFMD cases caused by additional viruses, including CV-A6 and CV-A10 (Aswathyraj *et al.*, 2016).

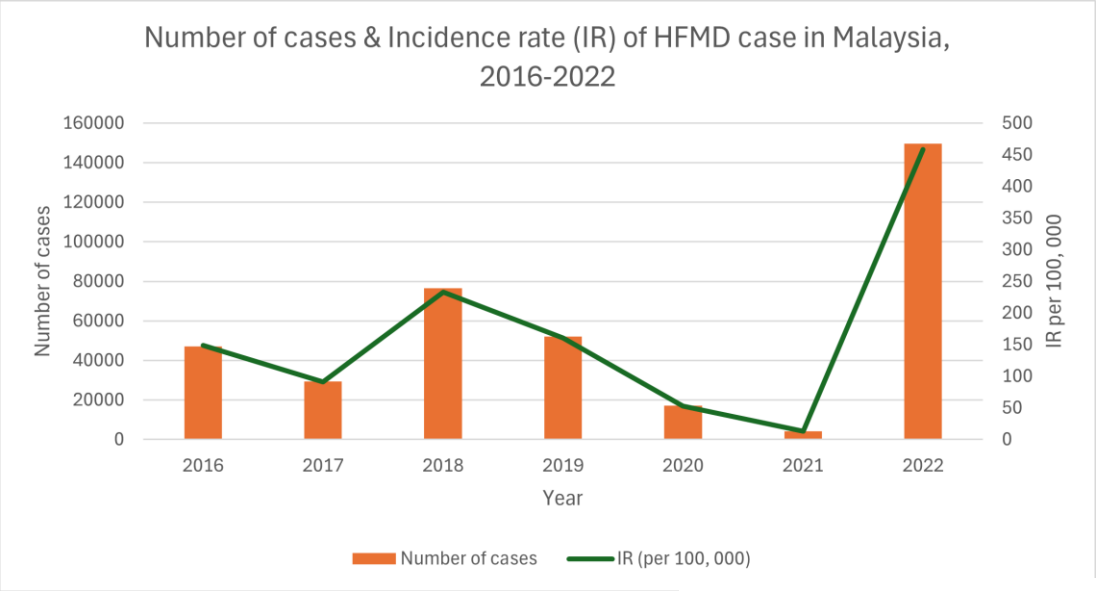
In response to the rising occurrence of HFMD in the Western Pacific Region, the World Health Organization (WHO) held an internal meeting from 2008 to 2009.

The purpose of this meeting was to establish a standardized surveillance system for HFMD outbreaks, which would be backed by laboratory diagnosis and response strategies. The resulting guideline has since been used as a reference by other countries to develop their own surveillance and response strategies (WHO, 2011). The HFMD surveillance system in Malaysia was initiated in 1997 following an epidemic in Sarawak. The requirement for HFMD notification has only been in place in October 2005, solely for administrative purposes. Nevertheless, it became compulsory to report all instances of HFMD and this requirement was implemented on 12 October 2006 via Act 342 Prevention and Control of Infectious Disease Act 1998 with amendment (PU. A 374/2006) due to the rising number of outbreaks and fatalities associated with HFMD (MOH, 2007).

In Malaysia, HFMD surveillance is conducted through two methods: clinical surveillance and laboratory surveillance. Clinical surveillance requires the compulsory reporting of all instances of HFMD within 24 hours after diagnosis, using CDCIS. Meanwhile, the monitoring of the laboratory was conducted by sentinel sites located in each state. Each state has a minimum of two sentinel sites that will send five specimens from five distinct patients per centre to a recognized laboratory for enterovirus surveillance (MOH, 2007). The assessment, prediction, and mitigation of the disease outbreak rely on these HFMD surveillances; hence they are crucial (Maddah *et al.*, 2023). An early warning surveillance system might be useful in containing an outbreak involving an institution if it were to occur.

Several factors, including the country's consistently high temperatures and humidity, its rapidly expanding urban population, and the significant amount of human interaction among children in overcrowded places like schools, daycares, and social

events, contribute to the recurrent outbreaks of HFMD in Malaysia. Despite the several strategies released by the Malaysian Ministry of Health to manage and contain the HFMD outbreak, the number of reported cases continues to climb annually. The incidence rate of HFMD cases reported from 2016 to 2022 is shown in Figure 1.1.



Source: MOH, Health Facts 2017-2023

Figure 1.1: Incidence rate of HFMD cases in Malaysia, 2016-2022

Regardless of the numerous efforts to manage HFMD infection, several obstacles persist. Given the absence of any targeted antiviral medication or vaccine for HFMD at present, relying only on public or parental knowledge and vigilance poses significant challenges as the primary option. Gaining insight into the dynamics of the HFMD virus, its epidemiological characteristics, and the related risk factors would aid in effectively reducing the impact of the disease.

1.2 Problem statements

Hand, Foot, and Mouth Disease (HFMD) remains a prominent public health concern in Malaysia, leading to recurrent outbreaks that affect many children annually. Acquiring knowledge about the patterns of disease occurrence and the factors that contribute to it, and applying suitable methods to control it, are crucial for properly managing this illness. Long-term public health efforts, together with scientific advancements, are essential for reducing the effect of HFMD in Malaysia and protecting vulnerable populations from this contagious disease.

The findings of this study will enhance our comprehension of HFMD cases in Malaysia, including the causes related to it. Furthermore, it would aid in the development of comprehensive strategies to efficiently mitigate the transmission of HFMD. At the same time, to accomplish one of the Sustainable Development Goals (SDGs) of ensuring a state of good health and promoting well-being for all individuals of all age groups (United Nations, 2015).

1.3 Study Rationale

The incidence of HFMD cases in Malaysia is steadily increasing each year, with the most recent incidence in 2022 were reported at 458.10 cases per 100, 000 population (Ministry Of Health, 2023). Various risk factors have been linked to the rise in the incidence rate of HFMD in Malaysia such as sex, age, temperature, humidity, rainfall and attendance to pre-school or nursery among others. However, there is lack of comparative analysis that had been carried out between two states in Malaysia. Both Kelantan and Penang are situated in the northern region of Malaysia. However, Penang has shown a greater incidence of Hand, Foot, and Mouth Disease

(HFMD) cases compared to Kelantan between 2021 and 2022 (Kelantan Health Department, 2022).

Therefore, the objective of this study is to investigate whether there are any disparities in the incidence rate and risk factors linked with HFMD patients between the states of Kelantan and Penang. The result of this study could contribute to a better comprehension of the risk factors linked to HFMD in the two selected states and aid in the development of a more comprehensive prevention and control strategy.

1.4 Research Questions

1. What was the overall incidence rate of HFMD cases between Kelantan and Penang from 2017 until 2021?
2. What are the differences in the distribution of HFMD cases among different age groups, genders, and races between Kelantan and Penang from 2017 to 2021?

1.5 Objectives

1.5.1 General objective

To estimate the incidence rate of notified HFMD cases and compare the distribution of HFMD cases for different age group, gender and race between Kelantan and Penang State in 2017 until 2021.

1.5.2 Specific objective

1. To estimate the overall incidence rate of notified HFMD case in Kelantan and Penang in 2017 till 2021.

2. To compare the distribution of notified HFMD cases for different age group, gender and race between Kelantan and Penang State in 2017 till 2021.

1.6 Hypothesis

1. There are significant differences between incidence rate of notified HFMD cases in Kelantan and Penang from 2017 to 2021.
2. There are significant differences in distribution of notified HFMD cases for different age group, gender and race between Kelantan and Penang from 2017 to 2021.

CHAPTER 2

LITERATURE REVIEW

The search of papers in this study was done using online search engine and database including PubMed, Science Direct, and Springer link. Several search strategies were applied, including the use of Boolean operators, “AND”, “OR” and “NOT”. The keywords used were hand, foot, and mouth disease, HFMD, risk factor and epidemiology.

2.1 Background

Hand, foot, and mouth disease or HFMD is a self-limited infection disease and is characterized by symptoms including fever and the formation of vesicular lesions on hands, wrists, feet, and mouth. HFMD caused by EV 71 is recognised for its heightened severity and potential to result in complication such as meningitis, encephalitis, and neurogenic pulmonary oedema. The HFMD outbreak in Taiwan in 1998 was the most extensive on record, with over 100,000 reported cases. Among these cases, 400 children were hospitalized as a result of central nervous system (CNS) involvement, and 78 children died from brainstem encephalitis with neurogenic pulmonary oedema (Ho *et al.*, 1999). In 1997, Malaysia saw its first occurrence of EV71, which led to the fatalities of 29 children aged below 6. The deaths were caused by the swift progression of heart failure and pulmonary oedema, which occurred following the children's hospitalization for a few days. The outbreak, which began in early April, has recorded a total of 2628 cases. Out of these instances, 889 children needed to be admitted to the hospital, and 39 people suffered from either aseptic meningitis or acute flaccid paralysis (Chan *et al.*, 2000).

2.1.1 Epidemiology of HFMD

Since the early 1970s, there have been multiple instances of HFMD outbreaks in children caused by EV 71 virus. These outbreaks are characterized by symptoms such as fever, skin eruptions on the hands and feet, mouth vesicles and severe cases involving the central nervous system or pulmonary edema. Within the Western Pacific Region, notable epidemics have occurred in countries such as Australia, China, Japan, Malaysia, and Singapore (WHO, 2011). The most reported causative agent of HFMD were EV 71 and CV A-16 prior to 2005. However, CV A-6 and CV A-10 have been reported to be more significant viruses that had been circulating and causing outbreak worldwide (Esposito and Principi, 2018; Zhu *et al.*, 2023).

The diagnosis of HFMD is made via a clinical assessment or by considering the epidemiological history of contact with infected individuals prior to illness. Additional tests may also be performed, such as blood serology, cerebrospinal fluid or swabs from mouth ulcers, rectal area, or blister for culture and sensitivity (MOH, 2007). The primary way of transmission for HFMD viruses are through direct contact with nasal and throat secretion, saliva, fluid from blisters, or feces of infected individuals (MOH, 2007; Zhu *et al.*, 2023). According to Koh *et al.* (2016) there are several papers that describe the incubation period for HFMD however, majority of it does not provide a source to justify the claimed period. In study conducted by Yang *et al.* (2017) in China, the incubation period distribution for different age groups was estimated. The findings revealed a median incubation period of 4.4 days (95% CI 3.8-5.1) for children aged 2-5 years old in kindergarten. This result aligns with the commonly cited range of 3-7 days found in various papers. Meanwhile, the estimated median incubation period of HFMD for secondary school students aged 12-18 years old was 5.7 days (95% CI 4-6

days). The virus can be identified in the pharynx and feces of an infected person several days before symptoms appear. The period of highest contagion occurs within one week following the appearance of symptoms (MOH, 2007; Cox and Levent, 2018; Zhu *et al.*, 2023). In Malaysia, as a child had been diagnosed with HFMD, it is necessary for medical personnel to notify all suspected or confirmed cases to the nearest District Health Office within 24 hours according to "Prevention and control of infectious disease Act 1988" . The reported case must meet the case definition of HFMD either based on clinical criteria or laboratory diagnosis criteria as outlines in the guideline (Malaysia, 2017).

HFMD has shown substantial epidemiological fluctuations worldwide in recent decades. The disease continues to be an endemic in certain countries of Asia, such as China, Japan, Taiwan, Singapore, and Malaysia with periodic outbreak throughout the years. The annual incidence of HFMD in China was 1.2 cases per 1,000 person-years. Out of all cases, 3.7% were confirmed through laboratory testing, and 0.03% resulted in death. In 2012, the highest incidence rate and mortality were observed in children aged 12 to 23 months, with 38.2 cases per 1,000 person-years and 1.5 death per 100,000 person-years respectively (Xing *et al.*, 2014). A recent study conducted by Wu *et al.* (2022) revealed that the annual incidence rate of HFMD in a Chinese province varied from 98.81 cases per 100,000 population in 2020 to 435.63 cases per 100,000 population in 2018. A study conducted in Singapore revealed that the annual incidence rate in 2001 was 125.5 cases per 100,000 individuals. This rate gradually rose to 435.9 cases per 100,000 population in 2007. The highest incidence rate was observed among children aged 0 to 4 years, with age-specific incidence rate that increased annually from 1460.5 per 100,000 population in 2001 to 5975.5 per 100,000 population in 2007 (Ang *et al.*, 2009). Meanwhile, Vietnam has consistently reported a high number of HFMD

cases each year since 2011, with an average of around 80,000 cases per year. The country experiences a major outbreak from 2011 to 2012, during which over 200,000 hospitalization and more than 200 deaths were reported. Recently in 2018, there were over 130,000 hospitalization and 17 deaths due to HFMD had been reported (Nhan *et al.*, 2020).

In 2017, Thailand reported a total of 70,377 cases of HFMD, with a prevalence proportion of 107.57 per 100,000 population and among these there were three fatalities reported. The Northern region of Thailand had the highest prevalence of HFMD at 129.06 cases per 100,000 population. The overall national incidence rate of HFMD for Thailand in 2016 was 78.46 cases per 100,000 person-years (Upala *et al.*, 2018). A five-year study conducted by Fong *et al.* (2021) in Sabah indicated that the annual incidence rate of HFMD from 2015 to 2019 range from 39.9 cases per 100,000 to 166.1 per 100,000 population, with an average annual incidence of 94.3 cases per 100,000 population across the five years. The latest reported incidence rate of HFMD in Malaysia for 2022 was 458.10 cases per 100,000 individuals, compared to 12.98 cases per 100,000 in year 2021. This demonstrates a significant surge in the number of cases within a one-year period (Ministry Of Health, 2022, 2023).

2.2 Risk factors of HFMD

The substantial increase in the incidence of HFMD is concerning, and the disease remains a significant public health concern due to its potential to cause fatality. Therefore, it is necessary to comprehend not only the causative agents but also the risk factors linked to the transmission of HFMD to implement effective prevention and control strategies. Multiple variables contribute to the occurrence and transmission of HFMD.

2.2.1 Age

In Singapore, Ang *et al.* (2009) study revealed that the incidence rate of HFMD was the highest among children aged 0 to 4 years old as it constituted 74.5% of reported cases in 2001. The same result shown in Guangzhou, China between 2009 to 2012 as there were a total of 166770 HFMD cases reported with 93.67% of cases were among children aged 0 to 5 years old (Li *et al.*, 2014a). Meanwhile, in Vietnam majority of HFMD cases reported were from children with median age of 18.7 months (Nhan *et al.*, 2020). In a study carried out in Malaysia, it was shown that the prevalence of HFMD among children under the age of 2 years old was consistently high from 2011 till 2014, The rates were 4.8 per 1,000 in 2011, 22.9 per 1,000 in 2012, 17.9 per 1,000 in 2013, and 20.6 per 1,000 in 2014 (NikNadia *et al.*, 2016). Another study in Kota Kinabalu, Sabah revealed that children aged six years and below accounted for about 93% of total cases reported in 2020 to 2018 with the highest incidence of 29% occurring among one years old children (Chin *et al.*, 2022).

2.2.2 Gender

There are several studies revealed that being male as one of the factors associated with HFMD infection. Study by Guo *et al.* (2022) show that the mean male-

to-female ratio was 1.47:1 with a higher prevalence of HFMD among male compared to female (χ^2=2188.249, $p < 0.001$). In an analysis conducted by Wang *et al.* (2018), it was found that the prevalence of male case of HFMD infection was 60% (95% CI: 59%-61%), while the prevalence of female cases was 40% (95% CI: 39%-41%). This indicates a male-to-female ratio of 1.5:1. Another study conducted in China indicated a higher incidence of cases in males than females, with a sex ratio of around 1.6:1. The sex ratio was also consistent between mild and severe cases, with more male cases than female cases each year (Wang *et al.*, 2017). The identical outcome was similarly derived from a five-year study conducted in Kota Kinabalu, Sabah, with male-to-female ratio of 1.3:1 (Chin *et al.*, 2022).

2.2.3 Race

Multiple studies have examined race as a contributing factor to HFMD infection. A study conducted in Singapore comparing the incidence rates across the three primary ethnicities in the country has revealed that the incidence rate among the Chinese is much greater than that among the Indians. During the study period in 2006 and 2007, the incidence rate of Hand, Foot, and Mouth Disease (HFMD) was greater among the Malay group compared to the Chinese group (Ang *et al.*, 2009). Furthermore, the seroprevalence of EV 71 among Malays was 34.9% (95% CI:29.7-40.6%), which was substantially higher than the seroprevalence among Indians (24.6%, 95 % CI: 17.8-32.9%) and Chinese (24.3%, 95% CI: 21.5-27.5%). However, there are no significant difference in the seroprevalence between the last two ethnic groups (Ang *et al.*, 2011).

A separate study conducted in Singapore found that 74% of HFMD cases were among Chinese ethnicity, while 15% were among Malay, 3% were among Indians, and the remaining 8% were among individuals of other ethnic backgrounds (Chen *et al.*, 2018). Meanwhile, the incidence of HFMD was highest among the Sabah indigenous

group compared to other ethnicity during the study period of five years (Chin *et al.*, 2022)

2.2.4 Pathogen characteristics

The Hand, Foot, and Mouth disease is caused by nonpolio enteroviruses, namely coxsackie A6, coxsackie A16, and enteroviruses 71, which belong to the *Piconaviridae* family of nonenveloped-RNA viruses. Global HFMD outbreaks might exhibit variations in terms of kind and geographical distribution. For instance, enterovirus 71 is the main causative agent in the Asia-Pacific region(Chan *et al.*, 2000). Yet, in Europe and the United States, coxsackievirus is predominantly associated with cases and outbreaks of HFMD (Mirand *et al.*, 2021; Yee, 2024). Given the extensive range of HFMD viruses that initiate global epidemics, there is a potential for the population to be reinfected more than once during their lifespans.

A study conducted by Chen *et al.* (2016) reveals that the reinfection rate is greater in males than in girls (OR 1.27, 95% CI: 1.21-1.32%, $p < 0.001$). Additionally, children who had previously been infected with the non-EV 71 virus have a higher rate of reinfection than those who had previously been infected with the EV 71 virus (OR 1.36, 95% CI: 1.02-1.80, $p = 0.034$). Nevertheless, within the same study, two patients were infected with EV 71 twice, with five and ten-months interval between each infection. A study conducted by Huang *et al.* (2013) further explained that the enterovirus 71 has several genogroups, and the genogroup B or C of EV 71 does not provide cross-protection against genogroup A. Thus, it is crucial to acknowledge that the diagnosis of HFMD does not rule out the possibility of re-infection in the future.

2.2.5 Type of residential area

The population density in a specific geographic region is a contributing factor to the incidence of HFMD. The study conducted by Qi *et al.* (2018) revealed that the

main urban areas in Chongqing had the highest concentration of HFMD cases. In Urumqi, China, a similar outcome was seen where the incidence rate of HFMD and the concentration of cases were shown to be greater in urban areas as opposed to rural areas (Gao *et al.*, 2021). Moreover, a study conducted by Wang *et al.* (2018) found that 65% of HFMD outbreak occurred in urban areas, with 95% confidence interval (CI) ranging from 48%-78%. In contrast, 35% of HFMD outbreak (95% CI: 22-52%) were reported in rural regions. A further study conducted among preschool children revealed that the incidence of HFMD patients is significantly greater in urban regions compared to rural ones ($p = 0.000$). Nevertheless, there is no substantial difference in the rate of case severity ($p = 0.471$) and case fatality ($p = 0.069$) between the urban and rural locations, as reported by Wang *et al.* (2017).

2.2.6 Children attendance to pre-school or nursery

A study by Zhu *et al.* (2020) found that the likelihood of children in kindergartens or attending preschool being infected was 2.22-3.43 times greater than children who do not participate in such institution. A study revealed a consistent decrease in the average number of HFMD cases when schools were closed, regardless of the reason for closure. It was observed that there was a 53% reduction (95% CI: 44%-62%) in cases during the week following a public holiday, and a 34% reduction (95% CI: 25%-43%) in the second week. However, no reduction in cases was observed in the third week after the public holiday (Chen *et al.*, 2018). The observed outcome may be attributed to increased social engagement among children attending preschool or nursery centres, as opposed to children who remain at home. Consequently, this interaction may have disrupted the transmission of HFMD viruses among the stay-at-home children.

2.2.7 Climate factors

There are numerous studies that had demonstrated there is correlation between the occurrence of HFMD cases with climate condition. The study published by Nguyen *et al.* (2017) in the Mekong Delta Region (MDR), Vietnam demonstrates that temperature, humidity, and rainfall are all highly associated with variations in HFMD occurrence. However, these associations exhibit various time lags over a week. According to the study, a rise of 1˚C in temperature correspond to a 5.6% increase in rate of HFMD after 5 days (95% CI:0.3-10.9). However, the increment of temperature was also related with a 4.7% drop-in rate of HFMD after 6 days (95% CI: -9.2-0.2). Meanwhile, an increase of 1% of humidity at a lag of 3 days and 6 days had a similar effect on the rate of HFMD that is 1.7% increase (95% CI: 0.7-2.7 and 0.8-2.6 respectively). An increment of 1 mm of rainfall was associated with a 0.5% rise in the rate of HFMD on both one-day and six-day delays (95% CI: 0.2-0.9 and 0.1-0.8 respectively). The HFMD incidence tends to increase from September and reach a peak in October to December which is the rainy season in the MDR then gradually decrease to the lowest level from June to August. In a study conducted by Hii *et al.* (2011), it was found that an increase of 1˚C in max temperature above 32˚C led to a 36% increase in the risk of HFMD incidence (95% CI: 1.341-1.389).

Additionally, an increase of 1 mm in weekly cumulative rainfall below 75mm resulted in a 0.3% increase in the risk of HFMD (95% CI:1.002-1.003). The study also reveals that the occurrence of HFMD in Singapore reaches its highest point during the warmer season of the year. Meanwhile, a study on predictive modelling conducted in Sabah investigated the correlation between the incidence of HFMD and fluctuations in temperature and demonstrated a weak positive correlation ($r_{0\text{-}3weeks}$: 0.17-0.22) with the most significant association observed during the initial week (Jayaraj and Hoe, 2022).

The fluctuation in HFMD incidence throughout the year can be attributed to the influence of environmental conditions, such as relative humidity, temperature, and type of surface contamination, on the stability of enteric viruses (Abad *et al.*, 1994).

2.3 Conceptual framework

The fundamental components of any infectious disease, including Hand, Foot, and Mouth Disease (HFMD), can be elucidated through the epidemiological triad. This triad comprises three primary components: the human or host, the agent, and the environmental aspect. The interplay among these three primary constituents would enable the transmission and occurrence of HFMD. The study's conceptual framework is grounded in the epidemiological triad, which is used to provide a more comprehensive understanding of the disease. During the literature study, many risk factors were identified and categorized under each of the three main components. The human or host characteristics included age, gender, and ethnicity. Regarding the agent component, the risk factors associated with it were the pathogen characteristics. Finally, environmental factors such as climate change, residential area type, institutions, and social contact are identified as risk factors for HFMD.

However, due limitation of secondary data that were used in this study, only several risk factors will be selected as mentioned in Figure 2.1 below. Factor with * and bold will be included in the study.

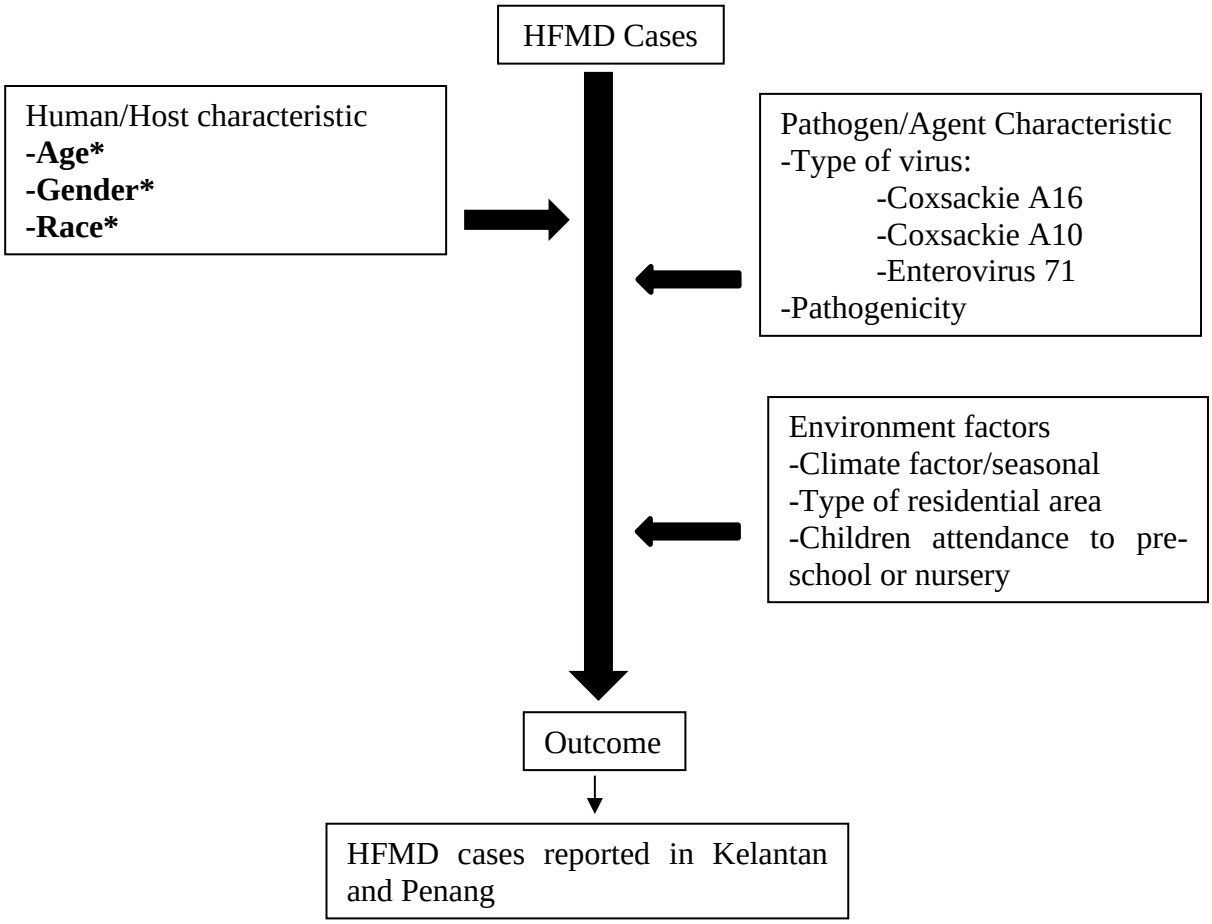


Figure 2.1: Conceptual framework for factor associated with HFMD case.

CHAPTER 3

METHODOLOGY

3.1 Study Design

This study is a comparative cross-sectional study of notified HFMD cases between the state of Kelantan and Penang.

3.2 Study Area

Two study areas are selected for this comparative study which are the Kelantan State Health Department and the Penang State health Department.

Kelantan is a state situated in the northeastern region of Peninsular Malaysia, covering a total area of 15, 040 square kilometres. It is comprised of ten districts in which consist of Kota Bharu, Pasir Mas, Tanah Merah, Tumpat, Kuala Krai, Bachok, Gua Musang, Jeli, Machang and Pasir Putih. According to Department of Statistic Malaysia (DOSM), it is estimated that Kelantan have a total of 1.93 million population as of 2021(Department Of Statistics, 2023a). Meanwhile, Penang is a state located in the northwestern coast of Peninsular Malaysia that is divided into two parts which is the island and Seberang Perai that separated by the Straits of Malacca. With an area of 1,049 square kilometres, it is estimated that the population of Penang state as of in 2021 was 1.77 million (Department of Statistics, 2023b).

3.3 Study Duration and timeline

This study took place from December 2023 till June 2024.

3.4 Reference Population

All notified HFMD case in Kelantan and Penang.

3.5 Source Population

All HFMD cases in Kelantan and Penang that had been notified using CDCIS e-Notification from 2017 to 2021.

3.6 Study Criteria

3.6.1 Subject criteria

All HFMD cases which had been notified via CDCIS e-Notification to Department of Communicable Disease Control (CDC) of Kelantan and Penang State in 2017 till 2021 fulfill inclusion and exclusion criteria.

3.6.2 Sampling frame

Sample for this study are obtained from reported cases of HFMD in both states from January 2017 till December 2021.

3.6.3 Inclusion criteria

All HFMD cases which had been notified via CDCIS e-notification to Department of Communicable Disease Control (CDC) Kelantan and Penang State starting from January 2017 until December 2021.

3.6.4 Exclusion criteria

Incomplete data in CDCIS e-Notification that is missing more than 10% data and unable to be verified further.

3.7 Sample size estimations

Sample size for each of objective are calculated as follows:

3.7.1 Objective 1

For objective 1 that is the incidence rate of HFMD between Kelantan and Penang, the sample size is determined by using a simple proportion formula where,

z = 1.96

d = 0.05

p = incidence of HFMD cases

Table 3.1: Sample size calculation for incidence of HFMD cases.

	z	d	p	n	n+10%	Reference
Incidence of HFMD	1.96	0.05	0.4581	381	419	Ministry Of Health (2023)

3.7.2 Objective 2

The sample size calculation for Objective 2 was performed for each variable associated with HFMD cases in Kelantan and Penang from 2017 to 2021. This calculation was done using the two-proportion formula and the Power and Sample Size calculation software. The variables pertaining to factors related with HFMD cases are displayed in Table 3.2. The sample size calculation involved the factors P0, P1, n, m, the significant level, and the power of the test. The sample size was determined for each variable, considering a 20% allowance for any missing data. Specifically, 10% was allocated for HFMD patients in Kelantan, and another 10% for HFMD cases in Penang. The following is a detailed explanation of each of these parameters:

P0 = proportion of HFMD in literature

P1 = proportion of HFMD in study

α = value of standard normal distribution cutting off probability α (1.96 for α = 0.05 (two-tailed))

β = value of standard normal distribution cutting off probability β (0.8 for 80% power of study)

m = ratio of size of exposed population to unexposed population

n= sample size for HFMD cases in Kelantan and Penang

Table 3.2: Summary of sample size calculation for some of the factors associated with HFMD cases

Risk factors	P0	P1	m	n	(nx2) +20%	Literature review
Age (less than 5 years old)	0.75	0.50	4	136	299	Ang *et al.* (2009)
Gender (male)	0.44	0.60	2	114	251	Zhu *et al.* (2020)
Race (Malays)	0.34	0.50	4	91	200	Ang *et al.* (2011)

Based on the above calculations, the smallest sample size required for estimation to be selected for enrolment is 419 samples. However, to ensure a comprehensive data analysis and accurate incidence rate estimation, in this population-based study, all HFMD cases reported in both states will be included.

Between 2017 and 2021, there were 7, 846 cases of HFMD reported in Kelantan. Penang, however, reported 10, 397 cases of HFMD. Therefore, to accurately demonstrate the occurrence of HFMD infection in both states, all cases from both states will be included in the study. Hence, the total number of samples would be 18, 243 samples.

3.8 Source of Data

This study involved secondary data collected from Communicable Disease Control Information System (CDCIS) e-Notification, managed by the Disease Control Division, Ministry of Health Malaysia. The data from CDCIS were downloaded in csv format that consist of 37 variables such as date of diagnosis, date of notification, address, age, gender, race, classification of cases, citizenship status, facilities reported, lab test carried out with date, district, latitude and longitude of case reported. However, there could be potential biases and limitation of using this secondary data from CDCIS as there could be inconsistency in data collection methods between two states and possibility of underreporting.

3.9 Definition of Operational Term

According to the Case Definition of Infectious Disease in Malaysia 3rd Edition, HFMD cases were defined according to clinical case definition and laboratory criteria for diagnosis (Malaysia, 2017).

Clinical case definition of HFMD is any child 10 years old and below with mouth or tongue ulcer and maculopapular rashes and or vesicles on palms and soles that with or without history of fever. However, a study conducted Yu *et al.* (2019) has shown that adults are also susceptible to HFMD infections. Therefore, for this study, the operational clinical case definition includes all cases of Hand, Foot, and Mouth Disease (HFMD) that meet the clinical criteria of having mouth or tongue ulcers, as well as maculopapular rashes and/or vesicles on the palms and soles. These cases may or may not have a history of fever, regardless of age.

Meanwhile the laboratory criteria for diagnosis for HFMD cases is any case that has clinical symptoms and positive for virus Coxsackieviruses A16, A5, A9, A10, B2, B5; and Enterovirus 71 and other enteroviruses which could cause HFMD, isolated or detected from stool or vesicle fluid or mouth ulcer or saliva. Outbreak of HFMD is characterized by the occurrence of two or more cases in the same locality within the incubation period of 6 days.

3.10 Data and statistical analysis

Objective one involves calculating the incidence rate of HFMD cases in both states using the formula shown in Equation 3.1.

$$\text{Incidence rate of HFMD in specified year} = \frac{\text{Number of new cases in a specified year}}{\text{Number of individuals in the population at risk in the specified year}} \times 1,000$$

Equation 3.1 Formula to calculate for incidence rate of HFMD cases in both states.

In addition, the age-specific incidence rate was determined using the method presented in Equation 3.2. The population at risk throughout the study period was obtained from the open data website of the Department of Statistics Malaysia (DOSM).

$$\text{Age-specific incidence rate} = \frac{\text{Number of new cases among individuals in the specified aged each year}}{\text{Total number of individuals in the specified aged in the same year}} \times 1,000$$

Equation 3.2: Formula to calculate the age-specific incidence rate of HFMD by years.